REMARKS

Summary of the Invention

The invention concerns recombinant HSV (claims 31-48, 54-67, and 73-74), viral stocks (claims 49 and 68), and compositions comprising recombinant HSV and a physiologically-compatible carrier (claims 50-53 and 69-72).

Discussion of Office Action

The Office Action rejects claims 1-2, 5, 9, 12-13, 15-16, 21-24, and 26-28 under 35 U.S.C. § 102(b) as being anticipated by Dong et al. (WO 95/06743).

The Office Action rejects claims 1-2, 5, 7-8, 12-16, 21-26, and 27-29 under 35 U.S.C. § 102(b) as being anticipated by Fraefel et al., *Mol. Med.*, *3*(12), 813-825 (1997).

The Office Action rejects claims 1-2, 5, 9, 12-16, 21-24, and 27-28 under 35 U.S.C. § 102(b) as being anticipated by Conway et al., *J. Virol.*, *71*(11), 8780-8789 (1997).

The Office Action rejects claims 1-2, 5, 7-8, 12-16, 21-24, and 27-29 under 35 U.S.C. § 102(b) as being anticipated by Johnston et al., *Hum. Gene Ther.*, *8*, 359-370 (1997).

The Office Action rejects claim 14 under 35 U.S.C. § 103(a) as being unpatentable over Dong et al. (WO 95/06743) in view of Glorioso et al. (U.S. Patent No. 5,998,174).

The Office Action indicates that claims 3-4, 6, and 10-11 would be allowable if rewritten in independent form.

Discussion of Claim Amendments

Claims 1-16 and 21-30 are cancelled, without prejudice, and claims 31-74 have been added. Claim 31 recites the features of cancelled claim 3 (in independent form). Claim 54 recites the features of cancelled claim 10 (in independent form). Claim 73 recites the features of cancelled claim 6 (in independent form). Claim 74 recites the features of cancelled claim 4 (in independent form). Support for the new claims can be found in the specification at, for example, page 4, lines 3-6, page 4, line 37- page 5, line 36, page 6, lines 16-31, page 7, lines 9-28, page 8, lines 17-19, page 8, line 33-page 10, line 8, page 10, lines 27-35, page 11, lines 1-26, page 12, line 8-page 14, line 11, and in the claims as originally filed.

The claim amendments add no new matter to the application. For the convenience of the Examiner, a marked-up illustration of the claims as amended is attached hereto, as is the text of all claims pending upon entry of the amendments set forth herein.

Discussion of Amendments to the Specification

The specification has been amended to correct obvious typographical errors (at page 3, line 19, and at page 7, line 34) and obvious grammatical errors (at page 5, lines 10-11, and at page 8, line 9). No new matter is added by way of these amendments.

Response to Claim Rejections

Applicants thank the Office for the indication that claims 3-4, 6, 10, and 11 would be allowable if rewritten in independent form. To advance prosecution, Applicants have rewritten dependent claims 3, 4, 6, and 10 in independent form (see new claims 31, 74, 73, and 54, respectively). Inasmuch as independent claims 31, 54, 73, and 74 are novel and unobvious, all pending dependent claims also are novel and unobvious. The rejections should therefore be withdrawn and the claims allowed.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: November 5, 2002

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: March 5 2002

PATENT
Attorney Docket No.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Glorioso et al.

Application No. 09/506,301

Art Unit: 1636

Examiner: G. Leffers, Jr.

Filed: February 17, 2000

For: ADENO-ASSOCIATED VIRAL GENE-TRANSFER VECTOR SYSTEM

ILLUSTRATION OF AMENDMENTS MADE IN RESPONSE TO OFFICE ACTION DATED JUNE 5, 2002

Amendment to the specification at page 3, lines 8-20:

U.S. Patent 5,856,152 describes a hybrid adenovirus-AAV vector including an ITR cassette within an adenovirus genome. While the system is apparently able to produce high-titer AAV stocks, it suffers from a number of drawbacks chiefly attributed to the properties of adenoviruses. For example, adenoviruses can be manipulated to carry only up to about 7.5 kb of exogenous DNA. Thus, where the rep and cap genes are introduced into the adenoviral genome, the carrying capacity of the ITR cassette is diminished. Deleting certain genes from the adenoviral genome can increase the carrying capacity of the vector; however, such gene products must be supplied *in trans* either to support adenoviral growth or to provide sufficient helper function to produce the desired AAV vector. Of course, such steps require either novel cell lines or secondary transfections to supply the deleted adenoviral genes, manipulations that [~~ted~~] tend to reduce AAV titer, as described above.

Amendments to the specification at page 4, line 36, through page 5, line 14:

While the HSV for use in the present invention is not an amplicon-based system, it can contain one or more mutations in HSV genes. Indeed, it is preferred that the vectors contain mutations in one or more genes essential for HSV replication so that such vectors are constrained to replicate as HSV viruses only in permissive cells. Any such mutation can be introduced into the HSV genome, many of which are known in the art (see, e.g., DeLuca, *et al.*, *J. Virol., 56*, 558-70 (1985), Samaniego *et al.*, *J. Virol. 69*(9), 5705-15 (1996); Field *et al.*, *J. Hygiene,*

81, 267-77 (1978); Cameron *et al.*, *J. Gen. Virol.*, *69*, 2607-12 (1988); Fink *et al.*, *Hum. Gene Ther.*, *3*, 11-19, (1992); Jamieson *et al.*, *J. Gen. Virol.*, *76*, 1417-31 (1995); Chou *et al.*, *Science, 250*, 1262-66 (1990); Sears *et al.*, *J. Virol.*, *55*, 338-46 (1985), U.S. Patents 5,658,724 and 5,804,413, and International Patent Application WO 98/15637). Such mutations can, for example, affect one or a combination of immediate early, early, or late genes[~~, or a combination thereof~~]. Desirably, the HSV backbone contains deficiencies in one or more essential genes to reduce toxicity within packaging and host cells (see, e.g., U.S. Patents 5,879,934, 5,804,413, and 5,658,724, all to DeLuca).

Amendments to the specification at page 7, line 29, through page 8, line 13:

Through the use of the inventive HSV, the invention provides a method of directing site-specific integration of an AAV-derived ITR cassette into a desired target DNA molecule, such as a chromosome within a host cell. In accordance with this method, the ITR cassette and the inventive HSV are introduced into the host cell. Expression of the rep gene(s) within the cell so as to deliver the active encoded rep protein(s) within the cell can effect excision of the ITR from the vector and, desirably, integration of the ITR cassette within the desired target DNA molecule. Of course, where the ITR is introduced into the cell within a larger polynucleotide vector (e.g., an extrachromosomal polynucleotide such as a plasmid or virus), the method further effects excision of the cassette from the vector. By virtue of the aforementioned inactivation of essential HSV genes, the method can facilitate the safe delivery of AAV-derived ITR cassettes for use in populations of host cells, which can be *in vivo* or *in vitro*. For example, the method can be employed to deliver genes to isolated $CD34^+$ lymphocytes *in vitro* which can then be employed in immunological protocols. An exemplary *in vivo* application could involve efficient delivery of active genes (e.g., encoding cytokines, a suicide gene, or other bioactive compound with antitumor activity) to dividing cells within a tumor. Additionally, where such host cells are mitotically-active, the ITR cassette (having integrated into the chromosomal DNA) will be retained by successive generations of mitotic offspring, whereas the HSV backbone will not, by virtue of its inability to replicate in the absence of the essential HSV genes.